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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,615	07/08/2003	Clemens Hendricus, M. Kocken	2183-6041US	8276

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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
11/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/615,615	KOCKEN ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-10,27-30 and 46-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-10,27-30 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/8/2009; 7/28/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Amendments to the Claims, filed 28 July 2009, have been received and entered. Applicant's Information Disclosure Statements, filed 28 July 2009 and 8 June 2009, have been received and entered. Claims 5-7, 11-26 and 31-45 are cancelled. Claim 49 is new. Claims 1-4, 8-10, 27-30, and 46-49 are pending and under consideration in this action.

Response to Amendment/Arguments

Any objections/rejections not explicitly repeated in this action are withdrawn herein.

Sequence Compliance

Applicants response filed 28 July 2009 made to the request for Sequence Compliance included in the previous non-final office action mailed 4/1/2009 is considered non-responsive because Applicant's reply stated the following:

> In response to the Office's comments with regard to Sequence Compliance, applicants respectfully reference the substitute Specification submitted February 17, 2005, wherein paragraph [0021] references the sequences depicted in Figure 1 as being SEQ ID NO:6. As the sequences were originally submitted in both electronic and paper format no substitute sequence listing should be needed.

Applicants reply has been fully considered but is respectfully not found fully responsive because Applicants response is directed to the nucleic acid sequence rather than to the amino acid sequence that is shown in Figure 1. The sequence identifier SEQ ID NO: 6 identifies the polynucleotide shown in Figure 1 but does not identify the polypeptide (amino acid sequence) shown in Figure 1. As stated in the previous office action regarding Sequence Listing Compliance, Figure 1 discloses **an**

amino acid sequence that is not properly identified with a sequence identifier (i.e. "SEQ ID NO:"). Sequence Listing, See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431.

In addition, additional amino acid sequences are disclosed in the specification (e.g. clean version of substitute specification filed 17 February 2005; page 5, ¶ 0011, line 4 and ¶ 0012, lines 5-6). The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02. If said sequences were originally submitted in both electronic and paper format, then applicant is only required to make proper amendment to the Brief Description of the Drawings (i.e. with proper sequence identifiers). However, if applicant has not previously submitted said sequences, then a new submission is also required (i.e. CD-ROM/CD-R, Paper Copy and Attorney Declaration).

In the interest of compact prosecution, this notice of non-compliance is being included in this office action on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-30, 47 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by claim amendments.**

Currently amended Claims 27 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are explained as the following: Claims 27 and 47 are directed to a method for producing a polypeptide (i.e. ectodomain/fragment). Claims 27 and 47, as amended, recite a step of expressing a nucleic acid into an ectodomain or fragment. The term "expressing a nucleic acid into a polypeptide" is confusing. It appears the method requires a step of expressing an mRNA into a polypeptide and a step of translating the mRNA into a polypeptide.

Claims 28-30 are indefinite insofar as they depend from Claim 27.

Newly added Claim 49 is indefinite in the use of the term "or" in lines 5, 7, 8 and 9 because it is unclear whether the limitations recited in lines 5-10 are required of both the ectodomain and the fragment thereof or are only required of either the ectodomain or the fragment and thus not actually required of either the ectodomain or the fragment.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8-10, 27-30, 46-48 STAND rejected and new Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record and presented herein. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants arguments have been fully considered but are respectfully not found persuasive because the MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not a sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, currently amended claims are drawn to a method for producing mRNA encoding a *Plasmodium falciparum* apical membrane antigen-1 (AMA-1) ectodomain or a fragment thereof in a yeast cell, said method comprising: providing said yeast cell with a nucleic acid encoding the ectodomain or the fragment thereof, wherein the ectodomain *comprises* amino acid sequences 25-545 of SEQ ID NO:7, and wherein the fragment thereof *comprises* an amino acid sequence from among 25-442, 97-442, and 97-545 of SEQ ID NO: 7, and wherein at least one glycosylation site has been removed from the ectodomain or the fragment thereof, and wherein the nucleic acid encoding the ectodomain or the fragment thereof has been modified to utilize the

yeast cell's codon usage, and wherein mAB 4G2 exhibits specificity for the ectodomain or the fragment thereof. In addition, newly added base Claim 49 is drawn to a method comprising: providing the yeast cell with a nucleic acid encoding a *P. falciparum* AMA-1 ectodomain or a fragment thereof, wherein the ectodomain **or** the fragment thereof comprises the amino acid sequence 97-442 of SEQ ID NO: 7, wherein at least one glycosylation site has been removed from the ectodomain **or** the fragment thereof, and wherein the nucleic acid encoding the ectodomain **or** the fragment thereof has been modified to utilize the yeast cell's codon usage, and wherein mAb 4G2 exhibits specificity for the ectodomain or the fragment thereof.

Thus, the nucleic acid biomolecules encoding the ectodomains and ectodomain fragments are a critical element to Applicants invention, as claimed, as directed to methods for producing mRNAs and ectodomains and ectodomain fragments. While Applicant shows written description for nucleic acids encoding the amino acid sequence of SEQ ID NO: 7 and the explicitly designated fragments thereof, Applicant does not show possession of the myriad of species encompassed by the claims which require unknown modifications to the amino acid SEQ ID NO: 7 or designated fragments thereof. The determination of which potential amino acid sequence modifications would be encompassed by the claim language requiring removal of glycosylation sites and correlate to the production of properly folded proteins that would be specifically recognized by the mAB 4G2 would not be predictable and would have to be determined empirically by experimentation involving live yeast cells.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the *entire scope* of the claimed invention.

Applicants response has been fully considered but is respectfully not found persuasive.

Applicants response is to traverse the rejection. Applicants submit that in view of the claim amendments, the claimed methods are in compliance with the Written Description requirement. Applicants note that "the Plasmodium falciparum AMA-1 ectodomain is expressly claimed as comprising amino acid sequence 25-545 of SEQ ID NO: 7". Applicants further note "that SEQ ID NO: 7 is not only illustrated in the sequence listing but also in FIG. 1". Applicants also note that the "ectodomain is further described in paragraphs [00091-00101] of the published application". Applicants additionally submit that "the Plasmodium falciparum AMA-1 ectodomain fragments, as presently included in the claimed methods, are in compliance with the Written Description requirement, as the fragments are expressly claimed as comprising amino

acid sequences 25-442, 97-442, or 97-545 of SEQ ID NO: 7." Applicants further submit that

> contrary to the Office assertions and in view of applicants' remarks presented in the response of July 3, 2008, which are incorporated by reference herein, the claimed fragments are sufficiently described by both structure and a correlation with the described structure and function. As previously noted, fragment structures are expressly claimed, to wit, "wherein the fragment thereof comprises an amino acid sequence selected from the group consisting of 25-442, 97-442, and 97-545 of SEQ ID NO: 7." Additionally, at least one exemplary nucleotide sequence for each of the three fragments are structurally disclosed in SEQ ID NO:6 and FIG. 1. The disclosed structures and sequences are further described in terms of function, to wit, "wherein said Plasmodium falciparum AMA-1 ectodomain fragment exhibits specificity for mAb 4G2."

Furthermore, Applicant argues that "[t]he Office alleges that 'the claims lack written description for that which encompasses critical sequences that are not known but which require experimentation to obtain due to the unpredictable nature of applicants' invention.'" Applicants disagree and submit that:

> The Specification describes amino acid residues that are important for such specificity for mAb 4G2. Paragraphs [0056]-[0062] of the published Specification describe experimental data that indicate that Pf3mH (presently claimed residues 25-442), Pf4mH, and Pfl4-0 (presently claimed residues 97-545) showed specificity with mAb 4G2, while others, such as Pfl0mH, PfgmH, etc. did not." See Specification at paragraphs [0056]-[0062]. The experimental data in the Specification shows that the epitope for mAb 4G2 was mapped to domain I or domain I+II. Id. The Specification additionally describes residues 97-442 as including domains I and II. Id. Thus, the Specification demonstrates that the fragments, 25-442, 97-442, and 97-545, as presently recited in the claims, are important necessary for specificity with mAb 4G2, as presently claimed.

In addition, Applicants argue that the teachings of Fandeur presented by the Examiner in the previous office action are not relevant regarding showing an unpredictable nature of applicants' invention. Applicants argue that "Fandeur teaches that two different variants of the Palo Alto strain of *Plasmodium falciparum* resulted in a

different immune response". Applicant further argue that "[t]he Office alleges that there can be strain specific or host specific immunity in a simian species infected with Plasmodium falciparum". Applicants submit that "this suggests, at the very most, the existence of some unpredictability between strains of Palo Alto strains of *Plasmodium falciparum* with regard to immunity for among different host or strains" and furthermore argue that "Fandeur provides no apparent suggestions of unpredictability in AMA 1 variants or in producing a properly folding protein" and argue that "Applicants' claims are related to methods for producing AMA-1 proteins and mRNA".

Furthermore, Applicants argue that

> even if Fandeur was relevant, which applicants dispute herein, any unpredictability between Palo Alto strains of *Plasmodium falciparum* is lessened in view of the Fandeur's disclosure that in several cases, pervious or concomitant heterologous infections indicated a degree of cross protection between the strains. Id. Moreover, Fandeur states that the monkey immune response to infection transcends phenotype antigenic variation and strain diversity. Id. Thus, even if Fandeur were relevant to the instant case, Fandeur at most suggests that while there may be some different effects by variants of different strains, there is predictability that transcends strain diversity.
>
> Applicants submit that in view of the preceding paragraph, at most Fandeur suggests minimal unpredictability between two strains of one type of *Plasmodium falciparum*. As previously stated, such a reference is, at most, distantly relevant if at all relevant to the currently claimed methods, as the claimed methods are directed to fragments of the AMA1 ectodomain. Furthermore, applicants have submitted herewith the following references (submitted in the enclosed IDS) which demonstrate and/or suggest the ability of recombinant expression of polymorphic and/or claimed fragments of *ama* I to yield properly folded proteins.
>
> - Remarque, E. J. et al. (2008), Infect. Immun. 76:2660-2670;
> - Malkin, E. M. et al. (2005), Infect. Immun. 73:3677-3685; and
> - Kennedy, M.C. et al. (2002), Infect. Immun. 70:6948-6960.
>
> As can be understood from the above references and the as-filed Specification, exploiting PCR primer sets presented in the as-filed Application, a real nucleotide sequences can be amplified from any *P. falciparum* strain or field isolate

> containing uncharacterized nucleotide polymorphisms. These nucleotide sequences can be optimized for *Pichia pastoris* codon usage (with deletion of potential glycosylation sites) according to the methods provided in the Specification, cloned into *P. pastoris* expression vectors and properly folded recombinant protein can be produced and purified following method described in the Application, without the need to have prior knowledge on the exact nature of the nucleotide polymorphisms and/or fragments. It is thus submitted that the presented claimed methods would more easily yield properly folded AMA1 proteins by following the methodology as presently claimed and described by the application. It is acknowledged that slight differences in antigeneity between the thus obtained proteins and the protein obtained by using the nucleotide sequences of Fig. 1 would be present, but these do not hamper the usability of the produced protein for an exemplary purpose in, e.g., a vaccine.

Therefore, Applicants conclude that "the claimed methods are sufficiently described by the Specification, as the claimed methods include multiple and express recitations of structure, such structure is demonstrated by the Specification as being important for functionality (e.g., specificity for mAb4G2), and as the evidence of record suggests there exists a degree of predictability such that a person of ordinary skill in the art could recognize applicants were in possession of the claimed fragments".

Applicants arguments have been fully considered but are respectfully not found persuasive. Specifically, Applicants argument stating that "as the fragments are expressly claimed as comprising amino acid sequences 25-442, 97-442, or 97-545 of SEQ ID NO: 7" is not persuasive and is not commensurate with the scope of the claims, as written. In particular, firstly, the newly added independent Claim 49 does not refer to any specific amino acid fragments and the claim encompasses any fragment of the ectodomain and secondly, the currently amended Claims 1-4, 8-10, 27-30, 46-48 do not recite fragments expressly claimed as comprising amino acid sequences 25-442, 97-442, or 97-545 of SEQ ID NO: 7 but encompass fragments with unknown modifications

for removing glycosylation sites. In addition, the claims are directed to nucleic acids that encode the ectodomain and/or fragments thereof and are not expressly directed at the polypeptide fragments. In addition, the claims require experimentation to determine which modified nucleic acids would encode modified polypeptides that would be folded correctly for specific recognition by the mAb 4G2. In addition, the claims use open claim language "comprising" and as such do not expressly limit the ectodomain fragments to the amino acid sequences 25-442, 97-442, or 97-545 of SEQ ID NO: 7 (or the modified amino acid sequences 25-442, 97-442, or 97-545 of SEQ ID NO: 7) but encompass additional unknown amino acid sequences in addition to the these amino acid sequences.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert
Examiner AU1636

/NANCY VOGEL/
Primary Examiner, Art Unit 1636